TSI 1355

Memorandum of Consultation

To: Janice Adams-King, Regulatory Project Manager
Division of Nonprescription Drug Products (DNDP)

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Re: Public communication about in utero acetaminophen exposure and the potential for adverse neurodevelopmental outcomes

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This memo responds to your consult regarding the clinical relevance of the published literature and the merit of updating public communication regarding prenatal acetaminophen (APAP) exposure and potential adverse neurodevelopmental outcomes in the offspring.

DBRUP CONSULT:

DBRUP reviewed the following:

- Integrated Tracked Safety Issue Memo (March 9, 2016)
- Division of Epidemiology I (DEPI I) Consult #1 (May 15, 2014)
- DEPI I Consult #2 (March 18, 2015)
- DEPI I Consult #3 (October 14, 2016)
- Drug Safety Communication titled "FDA Review of Possible Risks of Pain Medicine Use During Pregnancy" – January 9, 2015
- Selected published articles on perceived risks and risk communication regarding medication exposure in pregnancy
- Selected published literature relevant to DBRUP's consult

Regulatory Background:

The following section summarizes the pertinent regulatory history based on the Tracked Safety Issue Integrated Summary Review for TSI 1355 (March 2, 2016, Valerie Pratt):

- **May 15, 2014**: DNDP opened Tracked Safety Issued 1355 at the completion of the DEPI I's review of a publication by Liew et al. reporting a positive association between prenatal APAP use and attention deficit/hyperactivity disorder (ADHD) in the offspring (1).
- **May 15, 2014**: In the *first* consult response, DEPI I stated that the Liew et al. findings were noteworthy, given the frequent use of APAP in pregnancy. After

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reviewing two additional publications on the effect of prenatal APAP exposure on the offspring, DEPI I concluded that the available evidence is difficult to interpret, and recommended continued monitoring the safety signal as part of the FDA's ongoing safety evaluation of analgesic use in pregnancy.

- **January 9, 2015**: FDA issued a Drug Safety Communication (DSC) stating that the evidence on potential risks to the fetus exposed to prenatal analgesics, including APAP, was inconclusive and recommended that "how pain medications are used in pregnancy remain unchanged."
- **March 18, 2015**: In the *second* consult response, DEPI I completed a second review of the literature and surmised that "whether the association is causal in nature is still uncertain" and "preclinical data may be more informative in that regard."
- **February 8, 2016**: After review of the published nonclinical literature, the pharmacology/toxicology team concluded that the animal studies were not adequately designed and conducted to address the question posed by DEPI I, that behavioral responses in animals predictive of ADHD in humans are uncertain; therefore, additional animal studies to explore this safety question were unlikely to be informative.
- **March 2, 2016**: TSI 1355 was closed after DNDP, DEPI I, and the pharmacology/toxicology teams concluded that (a) the available data did not support a causal association between in utero APA exposure and ADHD in the offspring, and (b) FDA had informed the public of this issue in the January 2015 DSC.
- **October 14, 2016**: Subsequent to the TSI closure, DNDP requested another DEPI I consult to review a new 2016 publication in JAMA Pediatrics reporting an association between prenatal APAP use and behavior problems in the exposed offspring. After a literature search, DEPI I identified three additional recently published studies on prenatal APAP and neurodevelopmental outcomes. In the *third* consult response, DEPI I reviewed the four new articles, all published in 2016, on prenatal APAP and neurodevelopmental outcomes in the exposed offspring.

  Across the three consults, DEPI I has evaluated a total of eight observational studies that each examined different neurodevelopmental outcomes with prenatal APAP exposure. DEPI I acknowledged that these studies varied in quality and outcome measurements, and had limitations, including major confounders. However, seven of eight studies reported modest positive association between prenatal APAP exposure and adverse neurodevelopmental outcomes.

  Therefore, "based on the growing evidence of potential adverse effect of APAP on the exposed offspring, even in the absence of proof of causal relationship," DEPI I recommended that FDA update the public of the "possibility of neurodevelopmental harm to the fetus from maternal APAP use; that APAP should be used judiciously during pregnancy; that other analgesics are associated with more definite pregnancy risks, and that APAP may be needed as an antipyretic to reduce risks associated with maternal fever."

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II. DEPI consults - Publications reviewed

This section outlines findings from the three DEPI I consults. The discussion focuses on the most relevant strengths and limitations of the eight studies to inform the quality and strength of evidence of drug attribution.

IIA. DEPI I Consult #1 (May 14, 2014)

In this consult, DEPI reviewed the 2014 Liew et al (1) and two additional published studies reporting association of prenatal APAP and neurodevelopmental-related outcomes in the offspring. DEPI I stated the following:

"Liew et al conducted a prospective cohort study using data from the Danish National Birth Cohort, maternal interview data, and Danish administrative health care data. The authors interviewed pregnant women twice during pregnancy and once after pregnancy for APAP use and medical history. Assessed outcomes included ADHD-like behaviors based on maternal interview of the child's behaviors at age 5, HKD diagnosis and ADHD medication use beginning at age 7.

Mothers reporting any APAP use during pregnancy reported more ADHD-like behavior in the offspring compared to unexposed mothers (adjusted relative risk [aRR]=1.13, 95% CI=1.01-1.27). Women reporting any APAP use in pregnancy were also significantly more likely to have a child with an HKD diagnosis (aRR=1.37, 95% CI=1.19-1.59) or a child who used ADHD medications (aHR=1.29, 95% CI=1.15-1.44), compared to unexposed women. Associations for all outcomes were strongest for APAP use in multiple trimesters and for more than 20 weeks in pregnancy."

Strengths:

- Prospective study design and prospective ascertainment of exposure mitigate selection and information/recall bias.
- Positive association between reported APAP use in pregnancy and risk of ADHD-related outcomes in the offspring was consistently seen.
- The study's use of multiple endpoints from different data sources likely captured a spectrum of ADHD severity.
- Positive association was strongest with the longest duration of APAP use in pregnancy (>20 weeks).

Limitations:

- Residual and unmeasured confounding might explain the observed positive associations.
- The absence of information on APAP strength and number of pills taken precludes any meaningful interpretation of a dose-response relationship.
- The authors did not assess clinical ADHD diagnoses.

From a clinical perspective, we would like to expand on the aforementioned limitations:

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- Although the authors adjusted for several important confounders, we believe that there are limits to ability of statistics to neutralize the important differences between mothers who used APAP versus unexposed mothers. These differences include a higher prevalence of the following in the maternal APAP cohort compared to the total cohort: psychiatric illness, fever during pregnancy, muscle and joint disease in pregnancy, infection/inflammation in pregnancy. For example, children born to mothers with psychiatric illness may have unaccounted genetic disposition or adverse environmental factors in childhood that could contribute to the child's ADHD diagnosis.

- The evaluation for possible ADHD includes comprehensive medical, developmental, educational, and psychosocial evaluation (2). Thorough evaluation is necessary to confirm the presence, persistence, pervasiveness, and functional complications of core symptoms, exclude other explanations for core symptoms, and identify coexisting emotional, behavioral, and medical disorders. The evaluation includes review of the medical, social, and family histories; clinical interviews with the parent and patient; review of information about functioning in school or day care; and evaluation for coexisting emotional or behavioral disorders (3). The necessary information may be obtained in several ways, including in-person discussions, questionnaires, and web-based tools. Important aspects of the medical history include prenatal exposures (e.g., tobacco, drugs, alcohol), perinatal complications or infections, central nervous system infection, head trauma, recurrent otitis media, and medications. Information on family history is important, because ADHD has a strong genetic component.

  Liew et al. relied on self-administered questionnaires and national administrative data to assess the study outcomes. The potential for misclassification of this complex diagnosis exists when the cases are identified by surveys completed only by the mother; the validation of diagnostic coding obtained from administrative data is unclear; and prescription data do not always reflect true diagnosis. In clinical practice, not infrequently, medications may be prescribed on a trial basis, even when the diagnosis is unclear. Although it is unknown whether misclassification differentially impacts the study findings, uncertainties about the validity of the study outcomes call into question the ability to translate the study findings to clinical practice.

- The study lacked certain critical information. It did account for other medications or substances used in pregnancy. There was no information on family history; ADHD has a strong genetic component. Information about the overall health of the pregnancy and delivery, the child's health, and environmental influences between the offspring's birth until the assessment of ADHD was not available. Although such missing information may or may not differentially impact the study results, it makes it difficult to attribute the role of APAP to the study outcomes.

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DEPI also reviewed two additional studies that did not assess ADHD. The first study found no association between prenatal APAP and low Intelligence Quotient (IQ) and attention decrements (4), whereas the second study reported positive association between APAP and externalizing/higher activities levels in the offspring (5). Although the second study reported outcomes that appear to align with ADHD, we caution its worth of adding to the weight of evidence. "ADHD-like" behavior is common in healthy children and should not be considered as "pre-ADHD."

IIB. DEPI I Consult #2 (March 15, 2015)

DEPI I was consulted to review a study conducted in response to the 2014 Liew et al. publication. According to the DEPI I consult response:

The investigators analyzed the data from the Aukland Birthweight Collaborative Study to evaluate association between prenatal APAP exposure and subsequent behavior difficulties (6). Shortly after birth, mothers were asked on the use of the following medications in pregnancy: (a) anti-inflammatories, (b) aspirin-based analgesics, (c) "other" analgesics (this could include APAP), (d) antibiotics, and (e) antacids. Assessments included mailed questionnaires at age 1 year and study visits at 3.5, 7, and 11 years. Behavioral endpoints were assessed by the parent using the Strengths and Difficulties Questionnaire (SDQ) and the Conners Behavior Rating Scale (CBRS), when the child is 7 and 11 years old. Nearly half of the mothers in the study reported using APAP during pregnancy. DEPI I concluded that "Some differences in the rating scale scores between APAP-exposed and unexposed children were consistent with the direction of the finding in the 2014 Liew study, though the data could not provide a meaningful analysis of the risk of ADHD as a clinical disorder. The present study provides some level of support to the previously reported association, though whether the association is causal in nature is still uncertain."

Strengths:

- Prospective study with prospectively obtained information on exposure
- Adjustments for multiple confounders for ADHD
- Length of follow up time up to 11 years in the offspring

Limitations:

- Lack of assessment of clinical diagnosis of ADHD; the clinical relevance of the behavioral scale assessments (SDQ, CBRS) by the mother in relation to ADHD is unclear.
- Lack of information on family history of ADHD, prenatal exposure to other medications or substances, timing and dose of APAP exposure in pregnancy, and overall health of the pregnancy and delivery.
- Lack of information on the child's physical, mental, and psychological health and other important developments, and other environmental factors in childhood that may contribute to the child's assessments.

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IIC. DEPI I Consult #3 (October 14, 2016)

In this consult, DEPI I reviewed four new studies, published in 2016, on the association of prenatal APAP and neurodevelopmental -related outcomes in the offspring. An overview of these four studies follows:

- *Stergiakouli et al*. assessed behavioral problems identified on a parental questionnaire when the children were 7 years of age, and found that prenatal APAP exposure was associated with measures of behavioral difficulties, including hyperactivity (7).
- *Avella-Garcia et al*. assessed symptoms of ADHD and other behavioral problems at age 5, and found that prenatal APAP exposure was associated with more ADHD symptoms and more autistic symptoms in males (it appeared protective in females) (8).
- *Liew et al*. (2016) assessed IQ at age 5, and reported that IQ was lower in children with prenatal APAP exposure, though more so in the absence of maternal fever; APAP may have mitigated the effect of maternal fever on IQ (9).
- *Vlenterie et al*. assessed a variety of behavioral and developmental outcomes at age 18 months, and reported that delayed walking was associated with in utero APAP exposure (10).

These four studies and their strengths and limitations are summarily described below:

(a) Stergiakouli et al.

This was a prospective cohort study from the Avon Longitudinal Study of Parents and Children (ALSPAC) that evaluated data from approximately 8,000 mothers and children. Exposure was determined by self-report APAP use in the previous 3 months on questionnaires at weeks 18 and 32 gestation, and maternal and partner APAP use when child is 61 months (5) years. The study outcome the Strengths and Difficulties Questionnaire (SDQ) obtained from mother when child was 7 years old. Statistical analyses were based on outcomes meeting or exceeding predefined threshold values on the SDQ subscale. Covariates included maternal alcohol and tobacco use and psychiatric history, maternal reports of possible indications for APAP (i.e., infections, muscle and joint problems, migraine, or headache), and presence of selected ADHD "risk alleles" in mothers that had been genotyped.

The study reported that more mothers who used APAP, compared to non-users, had psychiatric illness (10% vs. 7%), higher smoking prevalence (21% vs. 17%), and alcohol use (60% vs 54%). The adjusted relative risk for the SQD total score (≥ 17) was nonsignificant for APAP use vs. no use reported at 18 weeks, but was 1.37 (1.07-1.75) for use reported at 32 weeks. The relative risks for SDQ hyperactivity scores ≥ 7 was statistically significant for APAP use reported at 18 weeks (1.18, 1.01-1.38) and at 32 weeks (1.22, 1.04-1.43). Although there were no statistically significant association with maternal postnatal APAP use, hyperactivity symptoms and conduct problems were significantly associated with partner's APAP use. In addition, the DEPI review stated that, "Linear regression analysis of SDQ scores as continuous variables showed statistically significant positive beta coefficients for 32 week APAP use on all SDQ

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scales, except prosocial behavior. However, maternal postnatal APAP use was also associated with statistically significant, positive beta coefficients on 4 of 6 SDQ domains."

Strengths:

- Prospective study design with prospective ascertainment of exposure
- Outcome assessment at 7 years of age when the child is older enough to manifest certain behavior more consistently.
- Evaluation of postnatal maternal and paternal APAP to control for some confounders

Limitations:

- There was no a priori primary outcome. The multiple hypotheses testing without adjustment for multiplicity introduces the risk of false positive association between APAP and the measured outcomes.
- Some findings undermined causal inference of prenatal APAP to the study outcomes. For example, hyperactivity symptoms and conduct problems were significantly associated with the partner's APAP use. Maternal postnatal APAP use was associated with statistically significant positive beta coefficients on 4 of 6 SDQ domains.
- There were imbalances in important baseline characteristics between mothers who used APAP versus those who did not. Although the study adjusted for these confounders, it is unlikely that statistical testing could entirely negate these important confounders.
- Information on the indication for APAP was not available, and confounding by indication could account for the study findings. The analysis did not examine dose or duration of prenatal APAP use.
- The use of the SDQ, a screening tool, to "diagnose" the study outcome is problematic. Per DEPI's review, the positive predictive value is only 35%. In addition, the correlation between SDQ scores and clinical psychiatric diagnoses are unknown. Lastly, mothers were the only source for outcome measurements, and these diagnoses require multiple informants evaluating the child in different context. Although these limitations may be non-differential, they significantly limit the ability to translate the study's findings to clinically relevant diagnoses.
- There was no information on family history of ADHD, overall health of the pregnancy and delivery, childhood environmental influences, or the child's co-morbid illnesses that could account for the study findings.

b. Avella-Garcia et al.

This was a prospective birth cohort study from Spain with the primary objective of evaluating "any adverse effects of prenatal APAP exposure on neurodevelopment at ages 1 and 5 years." Exposure to APAP was determined during interviews of mothers at weeks 12 and 32 of pregnancy. Mothers reported medications taken during pregnancy, or up to one month before pregnancy, and their indications; possible indications for APAP were analgesia, infection, or other. Outcome measures included the Bayley Scales of

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Infant Development (BSID) at age 15 months, and at age 5 years, the McCarthy Scales of Children's Abilities (measuring cognitive ability), the California Preschool Social Competence Scale (CPSCS), the Childhood Autism Spectrum Test (CAST), the Conners Kiddie Continuous Performance Test (K-CPT), and whether the child met Diagnostic and Statistical Manual (DSM-IV) criteria for ADHD.

A total of 2195 children were assessed at 15 months, and 2001 at age 5 years. Of the children in the sample at age 5, 41% had prenatal exposure to APAP. Analgesia accounted for 2/3 of the APAP indications. Compared to non-users, mothers who used APAP had more chronic illnesses, and were more likely to have smoked or had a fever during pregnancy. At 5 years, APAP exposed children had more DSM-IV hyperactivity symptoms (adjusted IRR 1.41, 1.01-1.98), but the association with total ADHD symptoms was nonsignificant. CAST measure of autistic symptoms was significantly increased in APAP-exposed male offspring (beta coefficient = 0.63, 0.09, 1.18), but was significantly lower in females ((beta= -0.51, -0.98, -0.05). On the other hand, some continuous performance measures showed greater deficits in females than males. Point estimates for DSM-IV ADHD symptoms were highest in subgroup of 5-year olds exposed in all 3 trimesters, although the IRRs did not reach statistical significance. There were no significant associations between prenatal APAP and cognition at 15 months (Bayley) or 5 years (McCarthy), motor development at 15 months (Bayley), or social competence score at 5 years (CPSCS).

Strengths:

- Prospective study with prospective ascertainment of exposure
- Assessment of exposed children to age 5 with various neurodevelopment assessments
- Information on the indication of use of APAP

Limitations:

- Lack of a priori primary analysis with multiple statistical testing
- Lack of details regarding cumulative APAP dose
- Lack of consistency of associations across the differential behavioral evaluations
- Inconsistent findings of positive associations on exposed boys versus girls in different assessments
- Unclear relationship between study outcomes and clinical diagnoses
- Mother who used APAP in pregnancy more likely to have chronic illness, smoked or had fever. Per DEPI's review, excluding mothers who had indications of chronic illness, analgesia, or fever during pregnancy from the age 5 subgroup did not materially change the results. Although the study adjusted for these confounders, statistically testing alone is unlikely to neutralize these differences. It is likely that mothers with these comorbidities, compared to those without them, have unmeasured genetic and/or environmental influences that could confound the outcomes measured in their offspring.

c. Liew et al. (2016)

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This was a population-based, prospective cohort study based on a substudy of the Danish National Birth Cohort in women with children aged 5 years. The objective was to assess the effect of prenatal APAP exposure on the offspring's IQ. Exposure to analgesics, including APAP, was obtained by telephone interview at gestational weeks 12 and 30, and at 6 months postpartum. Outcomes were based on psychologist-administered Weschler Primary and Preschool Scale of Intelligence-Revised to assess IQ at age 5.

Data were analyzed from approximately 1500 mother-child pairs. Mothers who took APAP in pregnancy were more likely to have used alcohol and tobacco, and were slightly more likely to report the occurrence of the potential indications for APAP use (fever, infection/inflammation, muscle/join pain during pregnancy). The authors found no differences between APAP exposed and unexposed offspring for total IQ, verbal IQ, or performance IQ. However, there was a significant adjusted mean difference in full scale IQ among children exposed during more than one trimester relative to unexposed children (mean difference -3.1, 95% CI -5.7, -0.45). Without APAP exposure, fever during pregnancy, but not muscle/joint disease or infection/inflammation, was associated with a significant mean full scale IQ decrease (-4.1, 95% CI -7.3, -0.9); APAP exposure appeared to modestly mitigate this effect.

Strengths:

- Prospective study with prospective ascertainment of exposure
- Outcome assessments conducted by psychologists
- Information on the occurrence of the potential indications for APAP

Limitations:

- Imbalances in the use of alcohol and tobacco between mothers who used APAP and those who did not
- Statistical imprecision, as demonstrated by wide confidence intervals
- Lack of information on specific indication for APAP use
- Lack of information on the overall health of the pregnancy and delivery, adjustment for developmental influences over the 5 years of childhood in assessing IQ

d. Vlenterie et al.

This was a prospective Norwegian Mother and Child cohort study using propensity score matching to assess neurodevelopmental problems following prenatal exposure to APAP in children at age 18 months. Exposure was obtained via questionnaires at gestational weeks 17 and 30, and at ages 6, 18, and 36 months postnatally. The questionnaires also asked for duration of use and possible indications of fever, pain, or infection. Outcomes were neurodevelopment assessment at 18 months, using the Ages and Stages Questionnaire (ASQ) for psychomotor milestones; the Emotionality, Activity, and Shyness (EAS) questionnaire for temperament; and the Child Behavior Checklist (CBCL) for behavioral problems. To adjust for confounding, the investigators calculated propensity scores using 23 maternal characteristics (e.g., maternal reports of alcohol, tobacco, depression, fever, infections, pain, concomitant medications during pregnancy).

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The investigators created propensity score-matched cohorts for APAP exposure < 28 weeks (N=13,503 pairs) and for APAP exposure 28+ days (N=1630 pairs).

The study findings were based on data from 51,200 children at age 18 months. Compared to non-users, more mothers who took APAP in pregnancy reported alcohol and tobacco use, depression, and concomitant medications. Prior to propensity score matching, compared to unexposed, more children exposed to APAP 28+ days had psychomotor (22% vs. 20%) and behavior problems (18% vs. 15%). After propensity score matching, the only statistically significant odds ratio was motor milestone problems (delayed walking) for which the OR was 1.35 (95% CI 1.07-1.70) with 28+ days exposure. There was no association with APAP use less than 28 days.

Strengths:

- Prospective collection on exposure and possible indications for APAP use
- Propensity score matching to adjust for confounders

Limitations:

- Lack of a priori outcome measure among the various assessment tested (multiplicity)
- Propensity matching size may not have provided sufficient power
- Neurodevelopment outcomes were assessed at 18 months, and the relevance of these assessments to neurodevelopment/behavioral disorders typically diagnosed at a later age (e.g., ADHD) is unclear.

III. Conclusions

DBRUP has conducted a high-level assessment of DEPI's consult reviews of a total of eight observational studies evaluating the association between prenatal APAP exposure and different neurodevelopmental outcomes in the offspring. Seven of eight studies reported a small, positive association between exposure and the outcomes of interest.

These studies, in general, have several noteworthy strengths. They are prospective cohort studies with prospective ascertainment of exposure, which mitigates the important problem of recall bias. Their large sample sizes are conducive to narrow risk estimates and provide statistical strength. To the extent possible, their analyses attempted to adjust for important potential confounders, such as maternal consumption of alcohol, tobacco and if known, indications of APAP use. When the information was available, the studies evaluated number of trimester of APAP use as a semi-quantitative surrogate of exposure/dose-response, and a trend in exposure/dose-response, especially with APAP use longer than 20 weeks, was observed in several studies.

On the other hand, all of these studies had significant limitations that question the causal effect of APAP on adverse neurodevelopmental outcomes. One critical limitation was the generally higher prevalence of alcohol use, smoking, or psychiatric/medical illnesses among mothers who used APAP compared to non-users. Although the studies attempted to adjust for these factors, it is unlikely that statistical adjustment alone could adequately

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correct for all confounders inherent to these factors. These attributes (smoking, alcohol use, and psychiatric/medical illnesses) may introduce unmeasured genetic disposition or environment influences that contribute to a child's neurodevelopmental outcome and account for the studies' findings. For example, children of mothers with alcohol abuse or with poorly managed psychiatric illness may grow up in a disruptive family environment that could contribute to the child's behavior problems. Maternal illnesses, smoking, and alcohol use could also adversely affect the pregnancy outcomes (such as intrauterine growth restriction with smoking), which in turn, could put fetal neurodevelopment at risk. The studies did not have a priori hypothesis, and multiple hypothesis testing unadjusted for multiplicity posed the risk that the studies' positive findings could be due to chance. And lastly, some studies reported certain findings that undermined the causal inference of APAP and the study outcome(s).

The studies lacked crucial information needed to independently evaluate the role of APAP in the outcomes measured. For example, ADHD has a weighty genetic component, and data on the family history of ADHD were not available. The studies also did not account for exposure to other medications, supplements or substances used in pregnancy. The indication for APAP use was not consistently available across the studies. In addition, there was no information on complications of the index pregnancy, such as hypertensive disorders or in utero infections, which may influence fetal neurodevelopment. Another shortcoming in all of these studies is missing information on the child's health conditions, and environmental and developmental influences during childhood. Most study outcomes were not clinical diagnoses, therefore their clinical relevance is unclear. The study outcomes were variable, and did not represent a common pathophysiologic grouping of neurological diseases. It should be noted that "neurodevelopmental" clinical disorders encompass a broad range of developmental deficits that produce impairments of personal, social, academic, or occupational functioning. These deficits vary from very specific limitations of learning or control of executive functions to global impairments of social skills or intelligence. Many of these diagnoses are also part of a syndrome, and are often not well-understood. Also, these disorders may be secondary to a variety of etiologies, including medical (e.g., epilepsy) or genetic condition (e.g., fragile X syndrome), or environmental factor (e.g., fetal alcohol exposure).

Without a clear understanding of the mechanism of APAP on the fetal brain, the studies' important limitations, and the absence of critical information on the index pregnancy and the child's environmental, developmental, and genetic influences, we believe that it is not possible to reliably attribute the role of APAP to the various neurodevelopmental outcomes measured in these observational studies.

In sum, we acknowledge the consistency of the findings of positive association between APAP and adverse neurodevelopmental outcomes in the majority of the published observational studies reviewed to date. Although we have more studies, we do not have higher quality data to better inform drug causality and what these findings mean in clinical practice. All of these studies had significant limitations, uncertainties, and critical missing information that preclude reliable inference of drug attribution. Thus, we

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are unable to draw any conclusion about the causal association between prenatal APAP exposure and the different adverse neurodevelopmental outcomes, based on the available evidence.

IV. Recommendations

DBRUP does not believe the available observational evidence merits updating the 2015 DSC titled "FDA Review of Possible Risks of Pain Medicine Use During Pregnancy" with more definitive conclusions, such as a "possibility" of causation, about drug causality of APAP and adverse neurodevelopmental outcomes. Nevertheless, we acknowledge the importance of apprising the public about FDA's review of new studies for a safety signal that was a subject of a DSC. Therefore, we believe it is reasonable to consider updating the 2015 DSC to indicate that FDA has evaluated additional publications on APAP and neurobehavioral/developmental outcomes in the offspring. The updated DSC, however, should retain the same FDA conclusion about the inability to draw reliable conclusions about drug causality and clinical recommendations stated in the 2015 DSC.

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